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Avoiding brain hypoxia in severe traumatic brain injury in settings with limited resources - A pathophysiological guide

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ABSTRACT

Cerebral oxygenation represents the balance between oxygen delivery, consumption and utilization by the brain, and therefore reflects the adequacy of cerebral perfusion.

Different factors can influence the amount of oxygen to the brain including arterial blood pressure, hemoglobin levels, systemic oxygenation, and transfer of oxygen from blood to the cerebral microcirculation.

A mismatch between cerebral oxygen supply and demand results in cerebral hypoxia/ischemia, and is associated with secondary brain damage and worsened outcome after acute brain injury. Therefore, monitoring and prompt treatment of cerebral oxygenation compromise is warranted in both neuro and general intensive care unit populations.

Several tools have been proposed for the assessment of cerebral oxygenation, including non-invasive/invasive or indirect/direct methods, including Jugular Venous Oxygen Saturation (SjO2), Partial Brain Tissue Oxygen Tension (PtiO2), Near infrared spectroscopy (NIRS), Transcranial Doppler, electroencephalography and Computed Tomography.

In this manuscript, we aim to review the pathophysiology of cerebral oxygenation, describe monitoring technics, and generate recommendations for avoiding brain hypoxia in settings with low availability of resources for direct brain oxygen monitoring.

1. Introduction

Traumatic brain injury (TBI) is one of the leading causes of death and disability in young adults [1]. TBI is characterized principally by two lesional mechanisms, primary and secondary injury [2]. Primary damage is the direct injury to the brain as a consequence of the initial impact, which can be both focal or diffuse [2]. Secondary brain injury may be caused by systemic (hypotension, hypoxemia) or intracranial events (intracranial hypertension, seizures) [2]. All these events result in the triggering of multiple pathophysiological phenomena that compromise the hydrodynamics, oxygenation and energy metabolism of cerebral parenchyma [3].

Ischemia plays a major role in the pathophysiology of TBI. Posttraumatic Ischemic damage is found on autopsy in >90% of fatal TBIs [4]. The brain has no capacity to survive without oxygen [5], and neuronal reserve is extremely limited.

Brain cellular metabolic activity and adenosine triphosphate (ATP) mitochondrial generation develops in an oxygen dependent environment [5]. ATP reserves need <1 min to be exhausted after complete cessation of flow [5].

Various physiological parameters participate in the supply and delivery of oxygen to the brain [5]. When the amount of oxygen supplied is insufficient or the cells cannot metabolize it for different reasons, we talk about tissue hypoxia [6]. Tissue hypoxia is a secondary insult with negative impact on clinical outcome [6]. For this reason, it is important to monitor and detect alterations in cerebral oxygenation [6]. To

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monitor the oxygenation status, different invasive technologies-such as the determination of hemoglobin saturation (Hgb) in the internal jugular vein bulb (SjO2); partial tissue oxygen pressure (ptiO2)- and non-invasive devices such as near-infrared spectroscopy (NIRS) [7] are available, however, none of these methods is of universal practical use or has been widely validated [7].

Additionally, all monitoring systems have limitations, including their cost and their unavailability particularly in regions with middle or low resources that have high prevalence of TBI [8]. The purpose of this manuscript is to provide the pathophysiological basis for the maintenance of acceptable cerebral oxygenation levels to avoid secondary brain hypoxia in the context of absence of advanced cerebral oxygenation monitoring. Our review is not to justify the inequity that separates higher from lower resources settings. We firmly believe that beneficial to patient technologies with reasonable cost to benefit ratios, should be widely available and every institutional and governmental effort should be made to obtain them.

2. Methods

We conducted a search of the literature using MEDLINE, EMBASE and Google Scholar databases. We searched for Medical Subject Heading (MeSH) terms and keywords including: “brain oxygenation”; “cerebral oxygenation”; “monitoring”; “neuromonitoring”; “brain hypoxia”; “management”; “cerebral tissue hypoxia”; “traumatic brain injury”; “head injury”; low middle-income countries” “low resources setting”. The search was limited to articles published in English from 1980 to today. Literature was presented, classified, and discussed by all authors. We reviewed the citations of included references to incorporate relevant studies that were not identified in our initial search.

2.1. Study identification and selection

2.1.1. Inclusion criteria

1) Population: adults (>18 years) severe TBI patients; 2) Intervention: cerebral oxygenation monitoring; 3) Setting: low resource or low-middle income regions. Classifying countries according to income follows World Bank categories based on economic considerations (https://datatopics.worldbank.org/world-development-indicators/stories/the-classification-of-countries-by-income.html).

2.1.2. Exclusion criteria

1) pediatric patients; 2) mild or moderate traumatic brain injury; 3) animal/in vitro studies; 4) experimental studies; 5) studies without cerebral oxygenation *monitoring*.

2.2. Definition of “limited resources”

Low- or middle-income countries, and corresponding levels of resources, are economic terms as defined by the World Bank in relation to per capita income [9]. In medicine there is no validated definition. In this sense, ``scarcity or limitation of resources “are relative terms in comparison with the extend of needs to be addressed [9]. Taking developed countries as “gold standard “, multiple levels of resource limitations exist in countries with low or moderate resources [9]. The Benchmark Evidence from South American Trials: Treatment of Intracranial Pressure (BEST:TRIP) trial, defined limited resources as absence of invasive intracranial pressure (ICP) monitoring [10]. In our opinion, a more global and specific definition of low resources applied to severe TBI would be one in which the chain of care is interrupted in one or more of its links, from prehospital care to rehabilitation programs [11].

3. Results

We did not find any study directed at the management of cerebral tissue hypoxia in adult patients with severe TBI in low-resource regions with or without specific monitoring of cerebral oxygenation.

4. Discussion

4.1. Cerebral oxygenation monitoring techniques and their limitations

After brain injury, the aim of any monitoring method is to provide information that helps to interpret pathophysiological mechanisms and assist in assessing responses to treatments [12]. No method of monitoring by itself i.e., uncoupled by the interventions undertaken, can improve outcomes; it is the information that when properly analyzed may really contribute [13]. It is important that the monitoring systems have an acceptable risk/benefit ratio, provide quality data that help in the evaluation of established therapies, as well as contribute to the prognostication process [13].

The Brain Trauma Foundation guidelines [14] recommended with low level of evidence cerebral oxygenation monitoring with either SjO2 or ptiO2 catheters whereas, the Neurocritical Care Society with the same quality of evidence recommends only ptiO2 monitoring in severe TBI [6].

The gold standard for the evaluation of cerebral oxygen utilization is positron emission tomography (PET), which is capable of simultaneously evaluating quantitative cerebral blood flow (CBF), cerebral blood volume (CBV), CMRO2 and oxygen extraction fraction (OEF); however, this technique is available to only a few select centers, and is not a means of continuous bedside monitoring [15]. Additionally, its implementation is complex, expensive, and mostly performed for research purposes [15].

Different types of cerebral parenchyma oxygenation monitoring have been in clinical use and are discussed below [6,16-20].

4.1.1. Jugular venous oxygen saturation (SjO2)

SjO2 is an invasive method popularized during the late 80s and early 90s[6], that allows a global evaluation of the state of cerebral oxygenation [16-18]. Exact catheter location and technique for positioning remains controversial. Continuous measurement via fiberoptic technology requires continuous calibration and is subject to multiple factors that decrease its reliability; intermittent measurements require accurate sampling technique to avoid extracranial contamination and availability of a co-oximeter for the accurate determination of venous saturation [6,16-18]. Being a measure of “global” oxygenation, values depend on multiple variables and do not provide adequate etiological insight for desaturations [16-18].

Mathematical formulations, that can be difficult to interpret, allow parameters such as arterio-venous oxygen content difference or arterial oxygen extraction to be obtained. However, such parameters have not gained wide clinical utility. Finally, SjO2 does not provide information from the posterior fossa and its insertion is not exempt from severe complications such as thrombosis [6,16-18].

4.1.2. Partial brain tissue oxygen tension (PtiO2)

PtiO2 is an invasive system, which only provides data about the availability of tissue oxygen, as average of supply and demand, and therefore its value depends on multiple variables [6,7,19-21]. PtiO2 does not provide the cause of alteration nor any further information about the metabolism or consumption of oxygen. It surveys a small volume of subcortical white matter (14–24 mm^2) [6,7,19-21]. It is expensive, requires adequate calibration and a stabilization time prior to analysis and the clinical evidence supporting routine use remains inconclusive [6,14].

4.1.3. Near infrared spectroscopy (NIRS)

NIRS is non-invasive; provides the oxygen saturation of hemoglobin in arterial, venous and capillary blood in the brain. It emits and detects beams of near infrared light (700 to 1000 nm) to penetrate through the layers of the surface of the head, including the scalp and skull. It is a

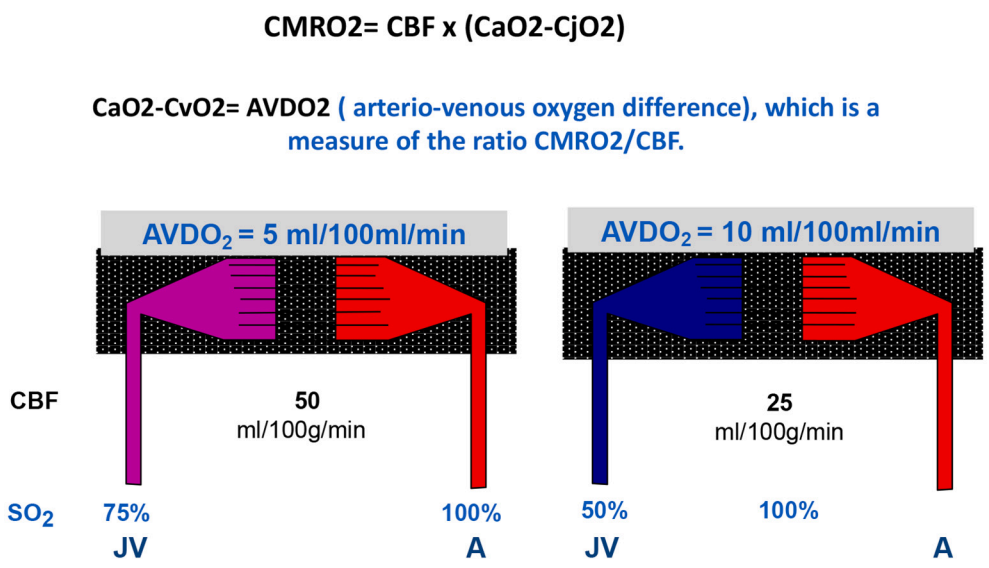

Fig. 1. Mechanism of SjVO2 measurement and interpretation.
Oxygen extraction in physiological and pathologic conditions. The cerebral metabolic rate of oxygen (CMRO2) depends on the cerebral blood flow (CBF) and the difference between the arterial and jugular venous oxygen content (CaO2-CjO2). In normal condition, with appropriate CBF (left panel), the arterial oxygen saturation is 100%, and the arterio-venous oxygen difference ($AVDO_2$) is 5 ml/100 ml/min, leading to oxygen saturation in the jugular vein of 75%. Under pathological conditions (right panel), when CBF is reduced, oxygen extraction from the brain is increased, thus leading to a reduction of the oxygen saturation in the jugular bulb to 50%.

promising technique; however, it has high cost and multiple limitations that prevent routine use [6,22].

First, NIRS is a regional method that is difficult to interpret, especially when it is used unilaterally [6,22]. Second, it depends on multiple physiological systemic and cerebral variables without the ability to directly detect the cause of its alteration [6,22].

Third, the measurements are subject to contamination by blood from extracranial sources [6,22]. Fourth, it does not have the ability to differentiate biomolecules with chromatic capacity such as Hgb and myoglobin [3,18].

Fifth, there are high rates of dispersion and misinterpretation when local tissues are altered by inflammation, edema and hematomas [6,22]. Sixth, the signal detected varies when there are perfusion disorders or changes in skin pigmentation [6,22].

Finally, it is vulnerable to interference as with changes in the intensity of ambient light or with signals from other equipment used in the intensive care unit [6,22].

4.2. Prevalence of brain oxygenation monitoring

The bibliography dedicated to this subject is scarce. A recent survey of intensivists from high-resource countries, reported a PtiO2 monitoring utilization rate of only 19% in centers of Canada, USA, and Europe [23]. Another, study from Spain revealed that the monitoring rate of cerebral oxygenation in severe TBI, specifically ptiO2, SjO2 and NIRS, was 8.6; 1.34 and 1.77% respectively [24]. Two North American studies in different time periods (2008–2016; 2013–2017) showed PtiO2 monitoring rates of 3.8 and 4.5%, respectively [25,26]. In a recently published survey of intensivists from the Latin American Brain Injury Consortium (LABIC), only 14.6% of responders indicated that they monitored brain oxygenation; half of them using jugular bulb oxygen saturation and only 2% among all responders using invasive brain tissue oxygenation monitoring [27].

4.3. Pathophysiology of Brain Hypoxia

4.3.1. Definition

Tissue hypoxia is a term that denotes cellular oxidative metabolism compromise either because the cell cannot metabolize oxygen, or insufficient delivery as compared to cellular demand [5-7,12]. Tissue hypoxia is a marker of shock states. If we extrapolate this concept to brain injury, cerebral hypoxia is synonymous to "brain shock" [15].

Brain tissue hypoxia can be defined according to available monitoring, *"If the SjO2 is < 50% or if the ptiO2 is < 20 mmHg we speak of global and regional hypoxia respectively "* [5-7,12]. Fig. 1.

Table 1
Cerebral hypoxia types based on Siggaard Andersen Classification.

`	CBF	$PbtO_2$	LPR	OEF	Pathophysiology
Ischemic	↓	↓	↑	↑	Inadequate CBF Low arterial PO_2 (hypoxemic hypoxia)
Low extraction	≅	↓	↑	≅	Low hemoglobin concentration (anemic hypoxia) Low half-saturation pressure P50 (high- affinity hypoxia)
Shunt	↑	≅	↑	↓	Arteriovenous shunting (microvascular shunt)
Diffusion	≅	≅	↑	↓	Diffusion barrier (intracellular or interstitial edema)
Uncoupling/ Cytotoxic	≅	≅	↑	↓	Mitochondrial dysfunction
Hypermetabolic	↑	↓	↑	↑	Increased demand

CBF, cerebral blood flow; ≅, no change or in either direction; LPR, lactate/pyruvate ratio; OEF, oxygen extraction fraction (SaO_2-rSO_2); P50, oxygen half-saturation of hemoglobin; $PbtO_2$, partial brain tissue oxygen tension; PO_2, arterial oxygen tension.

4.3.2. Causes of cerebral tissue hypoxia

The approach to brain tissue hypoxia must be based on pathophysiological reasoning [28]. According to Siggaard-Andersen there are different types of tissue hypoxia [29]. Table 1 From a practical point of view, it is possible to analyze the different situations following the *"oxygen route "*from the ambient air to its final destination, the mitochondria [7,12,15,21,28,29]. Fig. 2.

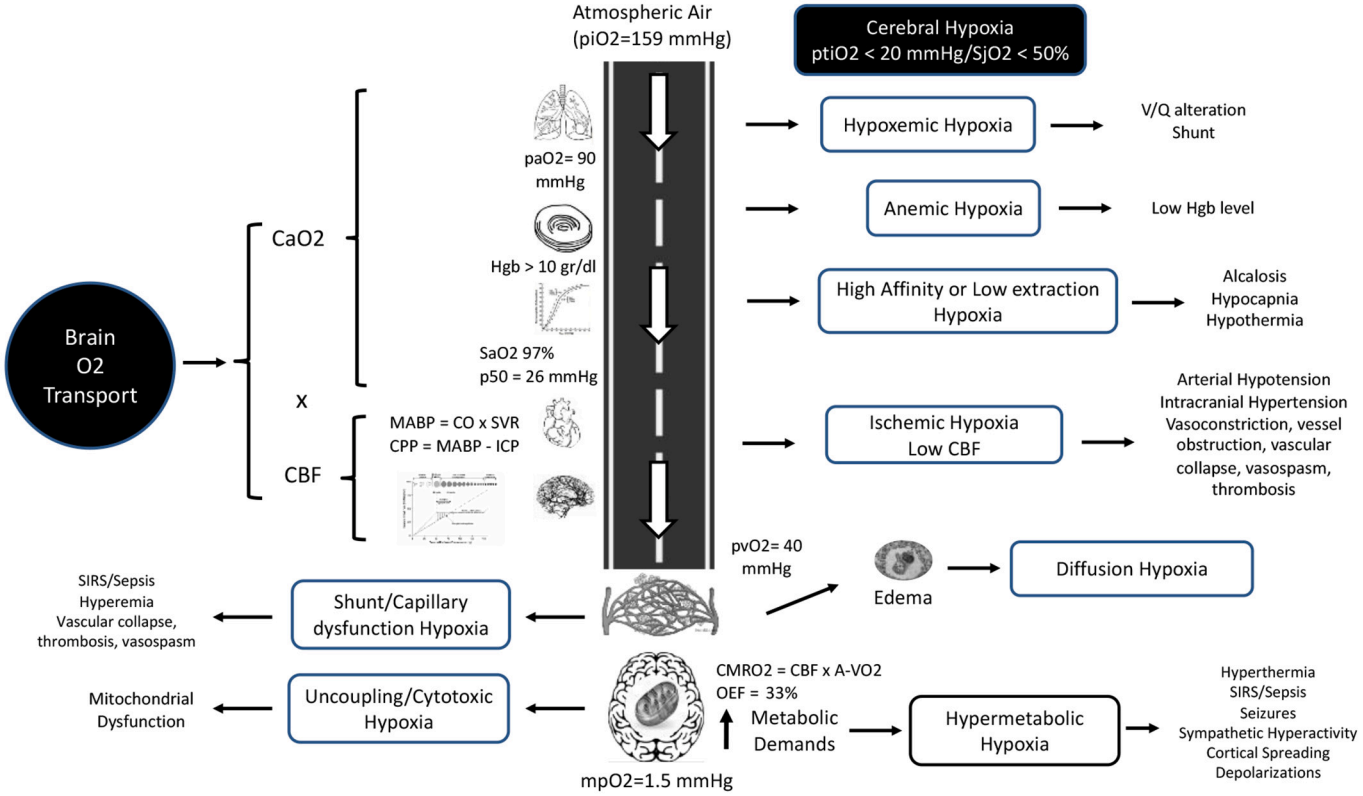

Fig. 2. Oxygen route. Pathophysiology of Brain Hypoxia: causes and types.
CaO2: arterial oxygen content; CBF: cerebral blood flow; paO2: arterial oxygen pressure; Hgb: hemoglobin; SaO2: arterial oxygen saturation; p50: arterial oxygen pressure at 50% hemoglobin saturation; piO2: inspirated oxygen pressure; pvO2: venous oxygen pressure; SjO2: jugular oxygen saturation; ptiO2: brain tissue oxygen pressure; mpO2: mitochondrial oxygen pressure; MABP: mean arterial blood pressure; CO: cardiac output; SVR: systemic vascular resistance; CPP: cerebral perfusion pressure; ICP: intracranial pressure; CMRO2: cerebral metabolic rate of oxygen;OEF: oxygen extraction fraction; V/Q: ventilation/perfusion ratio; CaO2 = (Hgb x 1,34 x SaO2) + (paO2 x 0.003).

a. Hypoxemic hypoxia: occurs as a consequence of the compromise of pulmonary gas exchange. Its marker is hypoxemia (decreased paO2 and SaO2) [4,5,8,12,15,28]. Pathophysiological reasons are disturbances in the ventilation-perfusion relationship or shunt fraction increase. Atelectasis, pulmonary contusions, pneumonia, ventilation induced lung injury and acute respiratory distress syndrome (ARDS) are the most common causes [7,12,15,21,28,29].
b. Anemic hypoxia: occurs when the amount or quality of Hgb is insufficient. The optimum level of Hgb to prevent cerebral hypoxia is unknown [30-32].
c. High affinity Hypoxia: the increase of the affinity of Hgb for oxygen is due to a left shift in the oxygen dissociation curve, making it harder to unload oxygen to the tissue. Its marker is p50 < 27 mmHg[7,12, 15; 21, 29]. Its causes are: hypothermia; alkalosis; hypocapnia (hyperventilation), and transfusion of prolonged-storage blood with depleted 2.3 DPG levels [7,12,15,21,29].
d. Ischemic Hypoxia: CBF is inadequate to meet brain tissue demands[7, 12 15, 21, 29]. Causes include inadequate CPP, cerebral vasoconstriction or flow obstruction [7,12,15,21,28,29]. CPP decreases as a consequence of systemic arterial hypotension or intracranial hypertension. In turn, hypotension may be caused by decreased cardiac output or systemic vascular resistance. Causes of cerebral vasoconstriction include hyperventilation, hyperoxia, drugs and vasospasm, whereas flow obstruction can be related to arterial dissection, arterial or venous thrombosis or endothelial edema [7,12,15,21,28,29].
e. Hypermetabolic Hypoxia: It occurs as a consequence of high metabolic demand, encountered with fever, seizures, systemic inflammation, sepsis, or paroxysmal sympathetic hyperactivity (PSH) [7,12,15,21,29]. Another cause is the presence of cortical spreading depolarizations and spreading ischemia phenomena [12,28].
f. *H*ypoxia due to opening of shunts [7,12,15,21,28,29,33,34]. It may occur due to: a) recruitment of non-functioning microvascular units; b) capillary dysfunction with new onset arteriovenous shunting; c) the increase in flow velocities from the arterioles to the veins, which decreases the time available for the exchange of oxygen between the blood and the cells [7,12,15,21,28,35,36]. These situations may be associated with arteriovenous malformations, hyperdynamic states (systemic inflammation, sepsis), cerebral hyperemia, intracranial hypertension, vasospasm, thrombosis of microcirculation or capillary collapse [7,12,15,21,28,33,34].
g. Diffusion Barrier Hypoxia: occurs because of the increase in the distance that oxygen must travel from vasculature to the cell [7,12,15,21,28,32-34]. Cerebral edema is the principal cause [7,15,21,28,29,35-37].
h. Cytotoxic or O2/ATP uncoupling Hypoxia: is the consequence of mitochondrial dysfunction secondary to the triggering of neurotoxic cascades (primary or post-ischemic mitochondrial failure), insufficient supply of energy substrate or sepsis [7,12,15,29].

4.3.3. *Etiology of brain hypoxia in clinical studies*

A cardinal study in patients with severe TBI established a close association between cerebral hypoxia and poor short-term outcome [38]. The association of tissue hypoxia with outcome was independent of ICP and CPP values. The causes of cerebral hypoxia in >90% of the cases were alterations in physiological variables such as: intracranial hypertension (50%), arterial hypotension (25%), hypoxemia (8%), hypothermia (7%), hyperthermia (5%) and anemia (2%). Only in 4% of the

cases, no etiology of hypoxia could be identified [38]. In another study, a quarter of the episodes of cerebral hypoxia were secondary to hyperventilation [39].

An analysis of two centers in patients with high grade SAH and multimodal monitoring have attempted to establish the burden of tissue hypoxia (ptiO2 < 20 mmHg) [40]. A quarter of the individuals presented one or more episodes of hypoxia [40]. To analyze the causes, the most frequent were: CPP <70 mmHg (27%), paCO2 < 35 mmHg (19%), paO2 < 80 mmHg (14%), Hgb levels <9 g/dL (11%), non-ischemic metabolic crisis defined as microdialysis-derived Lactate/pyruvate >40 and glucose <0.7 mmol/L (7%) and hyperthermia (4%) [40].

A recent study in post-craniectomy severe TBI individuals with controlled ICP showed a prevalence of cerebral tissue hypoxia of 14.6% [41]. When analyzing the causes; 17% were due to secretions in the airway, 10% to a decrease in CPP, 9% during mobilization while in 31% of cases, the cause could not be identified [41].

4.3.4. Brain hypoxia management and outcome in clinical studies

Cerebral hypoxia (PtiO2 < 20 mmHg) has been shown to be an independent.

predictor of unfavorable outcome in uncontrolled retrospective series [38,40,42]. Several cohort studies have shown an association between treatment of low PtiO2 with improved outcomes [42,43]. There have also been studies showing no clinical outcome benefits [42,44].

A recent phase II trial, the BOOST 2, was the first to show that the management of severe TBI guided by ICP and PtiO2 monitoring is safe and feasible and reduces the burden of tissue hypoxia as well as showing a tendency to decrease mortality and improve functional outcome [45]. Based mainly on this study and despite the lack of universal validation and the mixed results from available evidence, use of ICP/PtiO2 monitoring has been incorporated within clinical algorithms such as the recent Seattle International Consensus Conference [46]. Recently, a metanalysis showed that in severe TBI, PtiO2/ICP guided management was associated with reduced mortality but not with better functional outcomes when was compared to ICP alone, however the quality of evidence was very low [47].

Three randomized controlled trials of similar methodologic design-BOOST III, BONANZA and OXY-C are currently underway with the aim to study the impact of ptiO2 monitoring on outcome in severe TBI patients [48-50]. It should be noted that all aforementioned RCTs are taking place in high income and resources settings, making extrapolation to other settings questionable. We think that serious consideration should be given during study design about inclusion of patients from LMICs to increase external validity and generalizability.

4.4. Indirect tools that can guide cerebral hypoxia detection

4.4.1. Computed tomography (CT) scan

CT scanning does not quantitatively assess CBF or metabolism [51]. It is of low sensitivity and specificity for the diagnosis of ischemic hypoxia in early phases. Tomographic signs of established cerebral infarction manifest as hypodensities of the compromised territory; however, the “early ischemia” signs have not been studied in the context of severe TBI. There is no good tomographic-pathological correlation for focal lesions; however, in severe TBI, the graded severity of the CT scan upon admission has been correlated with the development of brain tissue hypoxia [52].

Typical tomographic findings of diffuse ischemic hypoxia are bilateral, symmetrical, and subtle, highlighting the loss of differentiation between the densities of the gray and white matter, hypodensity of the basal ganglia, hippocampus, cerebellum, and cortical gray matter, especially localized in peri-Rolandic and occipital areas [51]. Other signs described are a) Reversal sign: reversion of densities between gray and white matter; b) pseudo subarachnoid hemorrhage sign: greater attenuation of the basal cisterns and cortical sulci which falsely increase the density of the subarachnoid space simulating hemorrhage and c) the white cerebellum sign: caused by the protective redistribution of the CBF to the infratentorial space during circulatory arrest [51]. Computed tomography perfusion (CTP) is performed for physiological evaluation of the brain parenchyma in the setting of cerebral ischemia [53]. The physiological data derived from CTP are displayed in perfusion maps, including cerebral blood flow (CBF), cerebral blood volume (CBV), and mean transit time (MTT) [53]. It is important to note that despite limitations, serial CT scanning is an essential tool in the monitoring of patients with severe TBI. CT imaging together with clinical examination were the neuromonitoring tools in one of the groups (non-invasive ICP monitoring) in the cohort of the BEST-TRIP trial [10].

4.4.2. Transcranial doppler (TCD)

TCD sonography is a non-invasive technique, permitting frequent or continuous bedside measurements of blood flow velocity (FV) in the basal cerebral arteries [54].

It is a useful tool in the management of severe TBI as it can help to detect low flow (arterial hypotension, intracranial hypertension) and high flow states (hyperemia, vasospasm) also allowing the evaluation of cerebral autoregulation or vascular reactivity to changes in paCO2. It also allows the diagnosis of cerebral circulatory arrest [54]. Fifty-seven patients with severe TBI were evaluated by serial TCD during the acute phase, 33 of which were simultaneously monitored with ptiO2 in order to detect ischemic hypoxia as a consequence of low flow states (LFS) defined as mean velocities of the middle cerebral arteries (MCAV) < 35 cm/seconds [55]. The prevalence of LFS was 63%, especially in the first 8 h after the injury, and was associated with an increase in the pulsatility index, especially on the side of the injury. This pattern was correlated with a decrease in ptiO2 and poor outcomes [55].

Another study analyzed the relationship between bilateral middle cerebral artery (MCA) FVs and ptiO2 during a 5-day period after moderate and severe TBI [56]. On the first day after trauma, 34% of the measurements were collected during periods of hypoxia (ptiO2 < 20 mmHg), all of which were associated with FV <40 cm/second (positive predictive value = 100%) [56]. In this context, TCD can be considered as a helpful tool for the early screening for post-TBI ischemia [56].

Recently, the IMPRESS-2 study, a prospective, multicenter, international study was performed to determine whether TCD-derived ICP (ICPtcd) can be considered a reliable screening test compared to standard invasive ICP monitoring across acute brain injuries [57]. ICPtcd was calculated based in a mathematical model which comprises parameters derived from TCD FVs and arterial blood pressure as follow:

$$CPPe = MABP \times Vd/Vm + 14$$

$$ICPtcd = MABP–CPPe$$

where CCPe is estimated CPP, MABP is the mean arterial blood pressure and Vd and FVm are MCA diastolic and mean blood flow velocities respectively. The Negative Predictive Value of the index was elevated for all invasive ICP evaluated cohorts (ICP > 20 mmHg = 91.3%; > 22 mmHg = 95.6%; and > 25 mmHg = 98.6%), indicating high discriminant accuracy of ICPtcd in excluding intracranial hypertension [57]. The optimal index threshold for ruling out intracranial hypertension was 20.5 mmHg, with a sensitivity of 70% (95% CI 40.7–92.6%) and a specificity of 72% (95% CI 51.9–94.0%) with an area under ROC curve of 76% (95% CI 65.6–85.5%) [57].

4.4.3. Electroencephalography (EEG)

EEG has been reported as having an acceptable correlation with cerebral ischemia [58]. The EEG undergoes morphological changes that run in parallel with the changes in CBF. When CBF falls between 25 and 35 ml/100 g/min, the fast EEG frequencies, alpha (8–12 Hz) and beta (13–30 Hz) will be attenuated [58]. If the drop in CBF is further accentuated, the slow frequency waves, delta (0.5–3 Hz) and theta (4–7 Hz) are manifested [58]. Current recommendations for the use of EEG

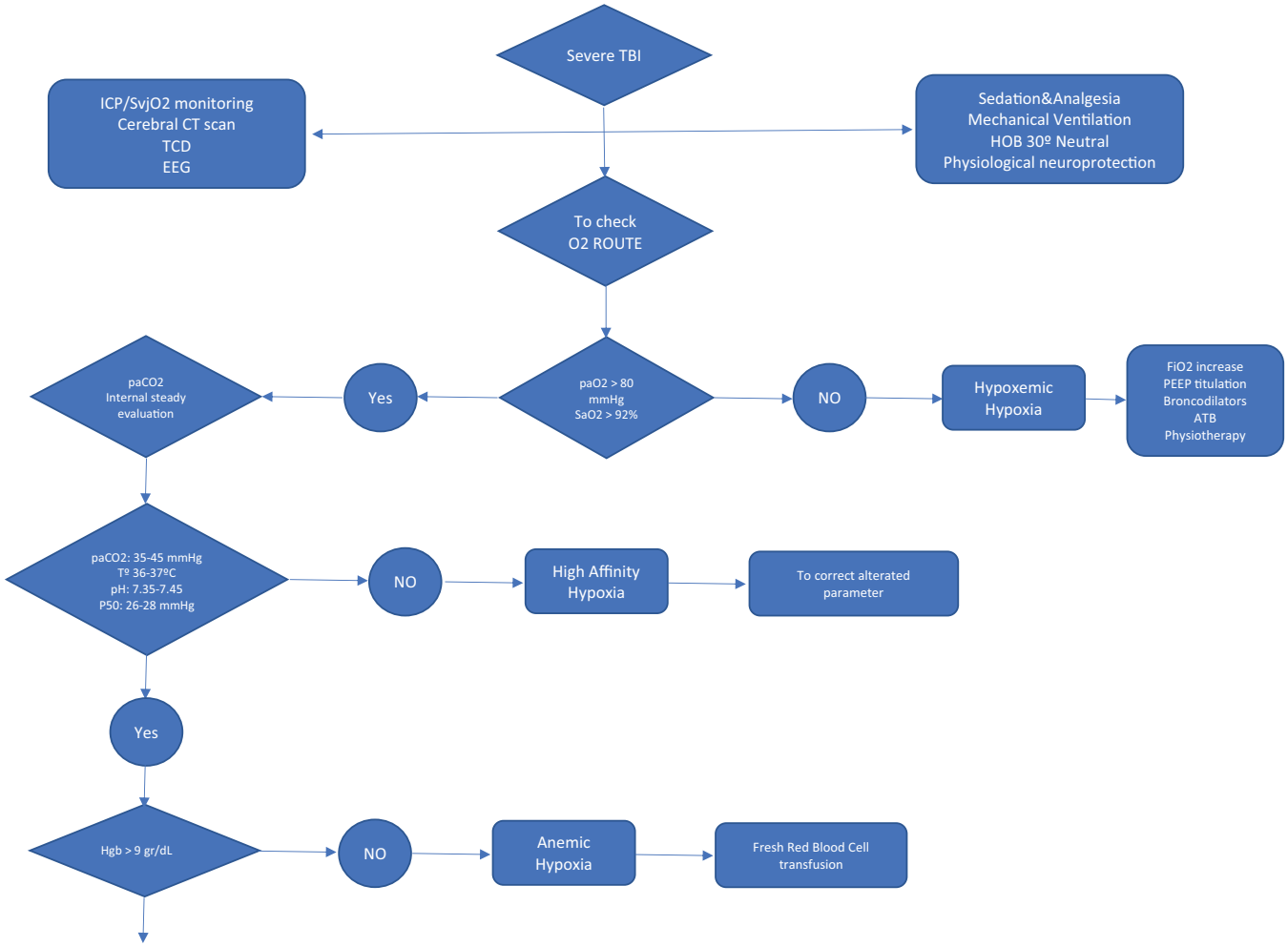

Fig. 3. Suggested Clinical Pathway to optimize oxygen delivery and to minimize the burden of brain hypoxia when specific and high technology monitoring of brain oxygenation is not available.
TBI: traumatic brain injury; LRS: low resource setting; MMCAv: mean middle cerebral artery velocity; *sec*: seconds; EEG: electroencephalography, CT scan: computed tomography; FiO2: oxygen inspirated fraction; PEEP: positive end expiratory pressure; ATB: antibiotics; SaO2: arterial oxygen saturation; paO2: arterial oxygen pressure; paCO2: arterial carbon dioxide pressure; T°: central temperature; Hgb: hemoglobin; p50: arterial oxygen pressure at half saturation of hemoglobin; CPP: cerebral prefusion pressure; MABP: mean arterial blood pressure; ICP: intracranial pressure; TCD: transcranial doppler; ICHt: intracranial hypertension; HFPD: high frequency periodic discharges.

for the detection and monitoring of ischemia are limited to aneurysmal subarachnoid hemorrhage (SAH) [59].

EEG monitoring during severe TBI should ideally be started during the period of greatest risk of ischemia, that is, the first 5 days, although there are no studies in TBI. Review and interpretation of the EEG should be frequent [58-60]. Recently, a study using continuous surface and cortical EEG recording in conjunction with multimodal monitoring in patients with poor-grade SAH established a close and temporal association between high-frequency periodic discharges (> 2 Hz and > 2 per second) and brain tissue hypoxia [61].

Since it is difficult to detect ischemia for long periods with regular EEG, the use of quantitative EEG is recommended [58-60]. Quantitative changes in the alpha-delta ratio are the most reliable neurophysiological indicator for the diagnosis of cerebral ischemia [58-60]. Claassen et al. showed that a 10% reduction in the alpha-delta ratio, compared to baseline, has 100% sensitivity and 76% specificity for the diagnosis of ischemia after SAH in the early period when the clinical-neurological examination is not possible or accurate [60].

4.5. How can we use alternative modalities to determine the type of brain hypoxia?

4.5.1. Ischemic hypoxia

TCD can detect states of low flow (<40 cm/s) associated with a decrease in MABP or it can indicate an increase in vascular resistance (pulsatility index >1.5) associated with intracranial hypertension. At the same time, it allows evaluation of cerebral autoregulation. Changes in the acoustic signals or in the morphology of the waves can indicate the presence of vasospasm or vasoconstriction. The use of Doppler in its M modality can help in the diagnosis of emboli or flow obstruction. Additionally, this type of hypoxia can be detected by EEG monitoring (alpha/delta ratio) and CT scan by evaluating signs of intracranial hypertension and cerebral edema (mass lesion, midline shift, effacement of sulci and/or basal cisterns).

Through current multiparametric monitoring, capnography, or laboratory analysis paCO2 levels can be monitored, while the echocardiogram provides data on hemodynamic parameters that could contribute to the drop in blood pressure (stress cardiomyopathy).

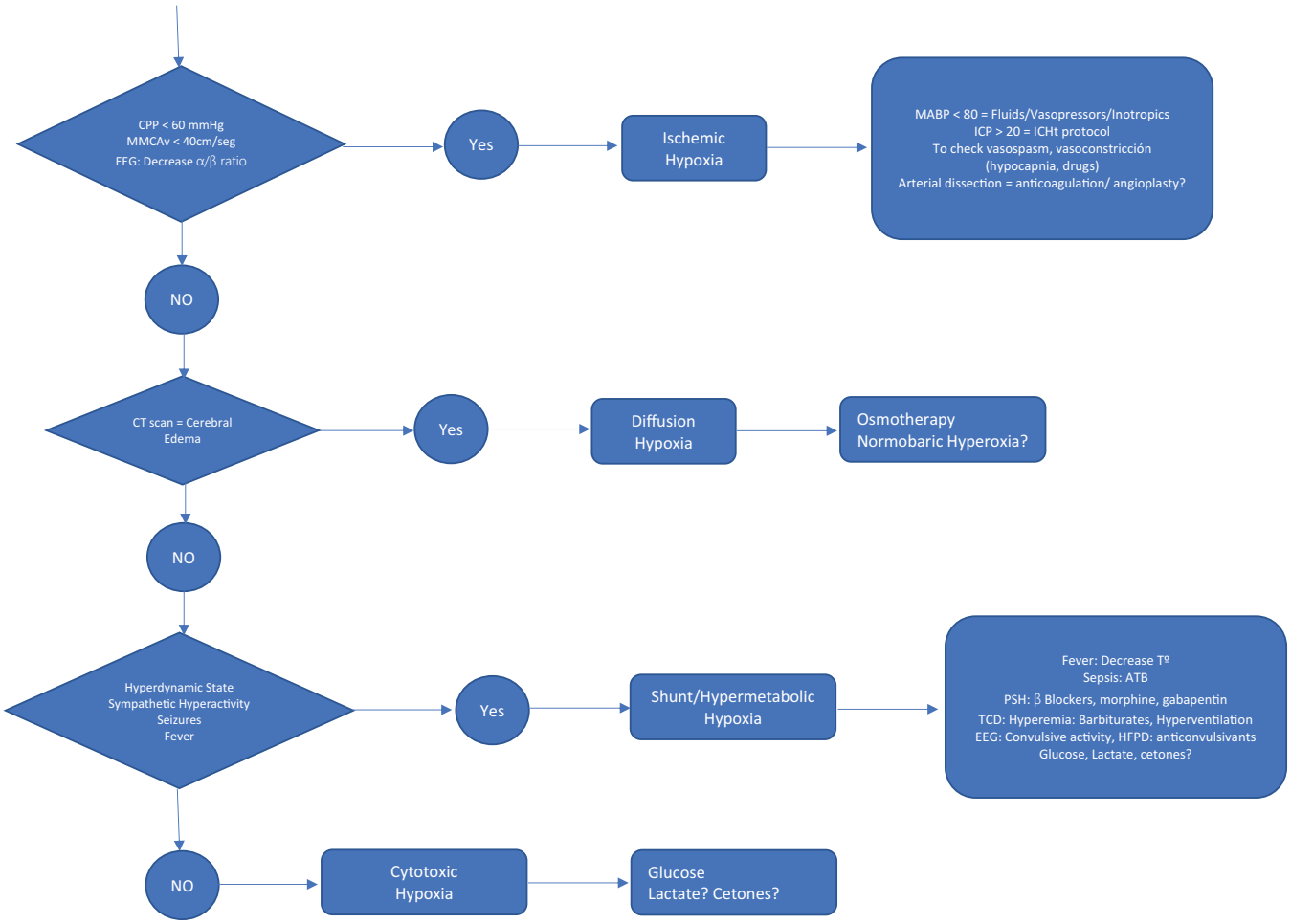

Fig. 3. (*continued*).

4.5.2. *Hypoxemic hypoxia*

Detectable with clinical examination, bedside monitor (SaO2), aided by blood gas analysis (PaO2) and plain chest radiography.

4.5.3. *Anemic hypoxia*

For its analysis it is only necessary to evaluate the levels of Hgb.

4.5.4. *High affinity hypoxia*

With the usual analysis of classic laboratory parameters (pH, paCO2) and clinical monitoring of core temperature, we come closer to an acceptable degree of certainty to determining the cause. Although not all equipment that analyze blood gases have this capacity, it is possible to analyze the p50 (26–28 mmHg), which will corroborate the situation of the Hgb dissociation curve.

4.5.5. *Hypoxia due to increased metabolic demands*

Clinical examination and temperature monitoring are essential. On the other hand, EEG monitoring becomes important for the detection of convulsive or non-convulsive states.

4.5.6. *Diffusion hypoxia*

In this type of hypoxia, cerebral CT scanning provides valuable information for edema detection. Blurring of cortical sulci, absence of differentiation between gray and white matter, ventricular compression, and absence or compression of basal cisterns are the classically described signs associated with cerebral edema.

4.5.7. *Shunt hypoxia*

It is difficult to recognize and diagnose even with ptiO2 monitoring. It is generally suspected in the presence of hyperdynamic states such as SIRS, sepsis, absolute or relative hyperemia with associated intracranial hypertension and after ruling out other causes of tissue hypoxia [28,62]. Cerebral hyperemia can be detected by TCD. The classic pattern is bilateral increase of MCA FVs associated with Lindergaard index <3 [63].

4.5.8. *Cytotoxic hypoxia due to mitochondrial dysfunction*

Requires cerebral microdialysis to diagnose, however it is important to bear in mind that mitochondrial dysfunction can occur without concomitant tissue hypoxia [64].

4.6. *Clinical approach to avoid brain hypoxia in settings with limited resources*

Based on the above analysis, most episodes of hypoxia are due to frequently encountered clinical situations that can be potentially prevented [38-41]. Based on this concept, to avoid brain hypoxia episodes and optimize oxygen delivery, we recommend certain clinical targets as delineated in Fig. 3. The target to be reached in the proposed algorithm is based on physiology [1,3,5,7,11-13,65] and current guidelines [14]. CPP above 60 mmHg (MAP>80 and ICP <20) together with MCA FV > 40 cm/seconds, are goals to achieve acceptable cerebral blood flow (CBF) levels [1,3,12,14,45].

Recently, recommendations suggested to achieve and maintain paO2 values between 80 and 120 mmHg [66], although other studies suggest a

threshold of 90 mmHg [67,68]. Hyperoxia is generally not recommended (except potentially in suspected diffusion barrier hypoxia) [69-71]. Intracranial hypertension should be managed according to the etiology [1,12,14]. Osmotic diuretics (mannitol, hypertonic saline) and normobaric hyperoxia (although controversial) with paO2 goals of 130–150 mmHg with FiO2 > 0.6 are alternatives for the treatment of diffusion hypoxia [72]. Avoiding fluctuations in body temperature prevents increases in ICP, increases the seizure threshold and maintains the dissociation curve of Hgb at an optimal state [1,3,12,14]. In general, paCO2 fluctuations should be avoided and a normocapnic range (35–40 mmHg) maintained [12,14,73]. The optimal Hgb level is unknown [32].

The response of PtiO2 to red blood cell transfusions it is not uniform and unpredictable [74,75]. In absence of brain oxygenation monitoring, it is reasonable to maintain Hgb levels around 9 g/dL, thereby ensuring adequate levels of the main oxygen transporter [32]. Transfusions of blood stored for long periods lacking 2,3 diphosphoglycerate, should also be avoided [5,31,76].

Adequate levels of sedation and analgesia help to reduce metabolic demands [1,3,12,14]. Anticonvulsants should be administered following current recommendations in high-risk individuals or upon detection of seizure activity [1,14].

5. Conclusions

In severe TBI, brain tissue hypoxia is a secondary insult with negative impact on tissue and patient outcomes. Therefore, it should be avoided or corrected as quickly and aggressively as possible. In situations where resources are scarce in terms of the technological means to monitor cerebral oxygenation, less expensive, readily available methods like EEG or neurosonography could be employed. A careful analysis of the physiology of the oxygen pathway and knowledge of the pathophysiology of the different types of hypoxia, could alleviate the burden of secondary brain injury and its consequences.

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Declaration of Competing Interest

None of the authors has any relevant conflicts of interest.

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